RHEUMATIC DISEASES AND THE EYE
Conflict of interest statement

I have no conflicts of interest to declare in relation to this lecture

• Clinical trials
  • Global Chief Investigator: Astra-Zeneca
  • Chief Investigator: TRACE RA (partly funded by Pfizer)
  • Principal Investigator: Roche, Pfizer, Abbvie, UCB, BMS, Novartis

• Unrestricted Grants
  • Pfizer, (Wyeth), Abbott (Abbvie)

• Honoraria for lectures / advisory boards
  • Roche, Abbvie, Pfizer, Novartis, UCB, BMS, Lilly, GSK, MSD, Genesis, Aenorasis

• Congress organisation
  • Abbvie, BMS, Genesis, MSD, Novartis, Pfizer, Roche, UCB, Aenorasis

• Hospitality
  • Roche, Abbvie, UCB, Novartis, Aenorasis
THE OPHTHALMOLOGIST’S VIEW

• SYMPTOMS (PAIN, PHOTOPHOBIA, DIPLOPIA, …)

• ANATOMIC CLASSIFICATION (LOCATION)

• ONSET

• LATERALITY

• DIFFERENTIAL DIAGNOSIS
  • INFECTIONS, MS, MALIGNANCIES, ...
  • RHEUMATIC DISEASES
<table>
<thead>
<tr>
<th>Ocular manifestations</th>
<th>Risk of vision loss</th>
<th>Rheumatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry eyes (sicca syndrome)</td>
<td>Low</td>
<td>Rheumatoid arthritis, Systemic lupus Erythematos, scleroderma, Sjogren’s syndrome</td>
</tr>
<tr>
<td>Keratitis</td>
<td>Moderate</td>
<td>Rheumatoid arthritis, Sjogren’s syndrome, Granulomatosis with polyangiitis</td>
</tr>
<tr>
<td>Scleritis</td>
<td>Moderate</td>
<td>Rheumatoid arthritis, Granulomatosis with polyangiitis, relapsing polychondritis</td>
</tr>
<tr>
<td>Uveitis</td>
<td></td>
<td>Seronegative spondyloarthritis, Behcet’s disease</td>
</tr>
<tr>
<td>Acute anterior uveitis</td>
<td>Low</td>
<td>Inflammatory bowel disease, Sarcoidosis</td>
</tr>
<tr>
<td>Chronic anterior uveitis</td>
<td>Moderate</td>
<td>Behect’s disease</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>High</td>
<td>Systemic lupus erythematos, Polyarthritis nodosa, Behect’s disease, Granulomatosis</td>
</tr>
<tr>
<td>Retinal vasculitis</td>
<td>High</td>
<td>with polyangiitis</td>
</tr>
<tr>
<td>Orbital inflammation</td>
<td>Low</td>
<td>Polyarthritis nodosa, Granulomatosis with polyangiitis</td>
</tr>
<tr>
<td>Optic neuropathy</td>
<td>High</td>
<td>Giant cell arteritis, Churg-Strauss syndrome</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>Common ocular manifestations</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>-------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Dry eyes, Scleritis, Peripheral ulcerative keratitis</td>
<td></td>
</tr>
<tr>
<td>Seronegative spondyloarthritis</td>
<td>Acute anterior uveitis</td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Acute anterior uveitis, Conjunctivitis</td>
<td></td>
</tr>
<tr>
<td>Reiter’s syndrome</td>
<td>Acute anterior uveitis, Scleritis</td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Acute/Chronic anterior uveitis</td>
<td></td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>Dry eyes</td>
<td></td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>Anterior uveitis, Retinal vasculitis</td>
<td></td>
</tr>
<tr>
<td>Behcet’s disease</td>
<td>Anterior uveitis, Vitritis, Periphlebitis</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Dry eyes, Eyelid discoid lesions, Retinal vasculitis</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus Erythematous</td>
<td>Ischemic optic neuropathy, Retinal vasculitis, Amaurosis fugax</td>
<td></td>
</tr>
<tr>
<td>Systemic vasculitis</td>
<td>Retinal arteriovenous anastomoses, Retinal neovascularization</td>
<td></td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>Hypertensive retinopathy, Retinal vasculitis, Cranial nerve palsies</td>
<td></td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td>Conjunctival injection</td>
<td></td>
</tr>
<tr>
<td>Polyarthritis nodosa</td>
<td>Scleritis, Peripheral keratitis, Orbital pseudotumor</td>
<td></td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RHEUMATIC DISEASES

- **INFLAMMATORY POLYARTHRITIS**
  - RHEUMATOID ARTHRITIS (RA)
  - PSORIATIC ARTHRITIS (PsA)
  - JUVENILE IDIOPATHIC ARTHRITIS (JIA)

- **SERONEGATIVE SPONDYLOARTHROPATHIES**
  - ANKYLOSING SPONDYLITIS (AS)
  - PSORIATIC ARTHRITIS (PsA)
  - REITER’S SYNDROME

- **AUTOIMMUNE DISEASES**
  - SJOGREN’S SYNDROME
  - SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
  - ANTIPHOSPHOLIPID SYNDROME (APS)
  - IgG4 RELATED DISEASES (IgG4RD)

- **SYSTEMIC VASCULITIC DISEASES**
  - ADAMANTIADES/BECHET’S DISEASE
  - ANCA ASSOCIATED VASCULITIS (WEGENER’S, CSS)
  - GIANT CELL ARTERITIS (GCA)
  - COGAN’S SYNDROME
  - RELAPSING POLYCHONDRIITIS (RP)

- **OTHER**
  - SARCOIDOSIS, IgG4 RD, PEMPHIGOID
  - HEREDITARY DISORDERS OF CTD
RHEUMATOID ARTHRITIS

KERATONJUCTIVITIS SICCA, SCLERITIS, EPISCLERITIS, KERATITIS,
PERIPHERAL CORNEAL ULCERATION
RETINAL VASCULITIS, MACULAR OEDEMA

• F>M /3:1
• 90% (DRY EYE SYNDROME)
• MORNING STIFNESS > 60 min
• SYMMETRICAL POLYARTHRITIS
• EXTRAARTICULAR INVOLVEMENT
RHEUMATOID ARTHRITIS

- Keratoconjunctivitis
- Iritis
- Scleromalacia (perforans)
- Sjögren's syndrome
- Lymphadenopathy
- Valve nodules
- Pericarditis
- Coronary arteritis
- Myocarditis
- Splenomegaly
- Carpal tunnel syndrome
- Skin ulcer
- Peripheral neuropathy
- Vasculitis
- Skin ulcer
- Rheumatoid nodule
- Myopathy
- Pulmonary fibrosis
- Pleural effusion
- Amyloidosis
- Osteoporosis
JUVENILE IDIOPATHIC ARTHRITIS (JIA)

• ASYMPTOMATIC IRITIS

• AGE<16yrs
• 3 TYPES
• RF(-)
• ANA
JUVENILE IDIOPATHIC ARTHRITIS

Fig. 1 Frequency of follow-up visits according to the varying risks of uveitis [ages of patients ≤6 years or >6 years refers at onset of juvenile idiopathic arthritis (JIA)] (RF −: negative rheumatoid factor; RF +: positive rheumatoid factor; ANA: antinuclear antibodies)
PSORIATIC ARTHRITIS

• Conjunctivitis, Uveitis, Keratitis

• M=F
• Inflammatory arthritis
• Skin, nails
• 60 – 70%: Skin psoriasis first
• 15%: Psoriatic arthritis first
• 15%: Skin and arthritis diagnosed at same time
• Dactylitis
• SpA
ANKYLOSING SPONDYLITIS

• UVEITIS, SCLERITIS

• M>F

• INFLAMMATORY BACK PAIN AND STIFFNES

• HLA B27
REITER’S SYNDROME

- Conjunctivitis, Uveitis, Keratitis
- Reactive Arthritis
- **Triad**: urethritis, conjunctivitis, arthritis
- M: 20 - 40 years old.
- 1-4 weeks after an infection
- **Infectious agents**: (Shigella, Salmonella, Yersinia, Campylobacter, Chlamydia)
- Family relatives affected by Reiter's syndrome.
- HLA-B27 association
- Keratoderma Blennorrhagica
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

- 20% of patients
- Keratoconjunctivitis sicca,
- erythematous conjunctivitis, uveitis, episcleritis, scleritis, keratitis, retinal hemorrhages,
- retinal vasculitis, proliferative retinopathy, optic neuritis,
- ischaemic optic neuropathy,
- hemianopia, amaurosis, internuclear ophthalmoplegia, pupillary abnormalities, oculomotor abnormalities, visual hallucinations... ...
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

• F>M
• The classic presentation of a triad of fever, joint pain, and rash in a woman of childbearing age should prompt investigation for the possibility of SLE
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
SJOGREN’S SYNDROME

• KERATOCONJUNCTIVITIS SICCA

• F>M 9:1
• AGE:30-50
• XEROPHTHALMIA (47%)
• XEROSTOMIA (42%)
• DYSPAREUNIA
• PAROTID GLAND ENLARGEMENT
• EXTRAGLANDULAR MANIFESTATIONS
ANTIPHOSPHOLIPID SYNDROME (APS)

- Vaso-occlusive retinopathy, ischemic optic neuropathy
- Amaurosis fugax, redness, pain, diplopia

<< arterial or venous thrombosis or specific pregnancy complications in women with laboratory evidence of antibodies to proteins bound to anionic phospholipids >>

40% SLE
ANTIPHOSPHOLIPID SYNDROME (APS)

• Preliminary criteria for the classification of the antiphospholipid syndrome*

  1. Vascular thrombosis
  • One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

  2. Pregnancy morbidity
  • (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
  • (b) One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency (18,19), or
  • (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
WEGENER’S GRANULOMATOSIS (GPA)

- Proptosis / exophthalmos, orbital cellulitis, uveitis, corneal ulcers, optic neuropathy

- Sinusitis, pulmonary nodules, uraemia

- Necrosis, vasculitis & granulomatous inflammation
WEGENER’S GRANULOMATOSIS
ADAMANTIADES BECHET DISEASE

- Uveitis, keratitis, scleritis and retinopathy, or optic neuritis.
- HLA B51
- Mouth & genital ulcers
- Skin
- Thrombosis
- CNS
- CVS
RELAPSING POLYCHONDRITEIS (RP)

- Keratitis, scleritis, uveitis, eyelid oedema, iritis, and retinopathy, ocular muscle paresis or optic neuritis.
- 85%-95% develop auricular chondritis.
- Unilateral or bilateral ear pain
- Nose, trachea, CNS, CVS
- Associated with systemic vasculitis, rheumatoid arthritis, SLE and Sjögren syndrome
COGAN’S SYNDROME

• Interstitial Keratitis (IK)

• “syndrome of non-syphilitic and vestibuloauditory symptoms”
• inflammatory eye disease and vestibulo-auditory symptoms
• progressive hearing loss, with or without vestibular symptoms
• young white adults
• systemic vasculitis, aortitis, musculoskeletal complaints, neurological symptoms, etc
GIANT CELL ARTERITIS (GCA)

AMAUROSIS FUGAX, RETINOPATHY, ANTERIOR ISCHEMIC OPTIC NEURITIS, OPHTALMOPLEgia

- Ocular involvement in about 25% of patients
- Begin treatment immediately with high dose corticosteroids daily. Do not wait for results of temporal artery biopsy

ACR Classification Criteria for Giant Cell Arteritis

1. Age more than 50 years;
2. New-onset headache;
3. Temporal artery abnormalities (e.g., irregularities of the arterial wall);
4. Erythrocyte sedimentation rate (ESR) greater than 50 mm/hour; and
5. Histologic evidence of arteritis on temporal artery biopsy (e.g., mononuclear cell infiltration or granulomatous inflammation).
SARCOIDOSIS

• Uveitis
• Orbital and adnexal involvement by a mass
• Proptosis and diplopia.

• F: 20-50 yrs
• More common in blacks and Asians
• Idiopathic multisystem disorder
• Characterised by non-caseating granulomata
SARCOIDOSIS

• **Heerfordt’s syndrome** (uveoparotid fever) is characterized by the combination of anterior uveitis, parotitis, fever, and facial nerve palsy.

• **Lofgren’s syndrome** is the constellation of erythema nodosum, hilar lymphadenopathy, fever, and migratory polyarthralgias.
SARCOIDOSIS

Organs Involved in Sarcoidosis or Sarcoid

- Brain
- Trachea
- Lungs
- Bronchi
- Heart
- Liver
- Spleen
- Skin
IgG4 RELATED DISEASES

- IgG4-related disease is a recently recognized condition (2003)

- IgG4-related disease is therefore analogous to sarcoidosis, another systemic disease in which diverse organ manifestations are linked by the same histopathological characteristics.

Table 1. Previously Recognized Conditions Now Acknowledged to Fall within the Spectrum of IgG4-Related Disease.

Mikulicz’s syndrome (affecting the salivary and lacrimal glands)
Küttner’s tumor (affecting the submandibular glands)
Riedel’s thyroiditis

Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)
Inflammatory pseudotumor (affecting the orbits, lungs, kidneys, and other organs)

Mediastinal fibrosis
Retroperitoneal fibrosis (Ormond’s disease)
Periaortitis and periarteritis
Inflammatory aortic aneurysm
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
## IgG4 RELATED DISEASES

**Diagnostic criteria for IgG4-RD (modified after Umehara et al. (22))**

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Diagnosis of IgG4-RD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ involvement: dysfunction, localized or diffuse swelling</td>
<td>Serum IgG &gt;135mg/dl</td>
<td>Histopathology*: IgG4/IgG Ratio &gt;0.4 and &gt;10 IgG4+ cells per HPF</td>
<td>Definite</td>
</tr>
<tr>
<td>Organ specific criteria for IgG4-RD (e.g. AIP, Mikulicz' disease)</td>
<td>Definite</td>
<td>Probable</td>
<td>Possible</td>
</tr>
<tr>
<td>Organ involvement: dysfunction, localized or diffuse swelling</td>
<td>Serum IgG &lt;135mg/dl</td>
<td>Histopathology*: IgG4/IgG Ratio &gt;0.4 and &gt;10 IgG4+ cells per HPF</td>
<td>Definite</td>
</tr>
<tr>
<td>Organ involvement: dysfunction, localized or diffuse swelling</td>
<td>Serum IgG &gt;135mg/dl</td>
<td>Histopathology: Not available or not diagnostic</td>
<td>Possible</td>
</tr>
<tr>
<td>Organ involvement: dysfunction, localized or diffuse swelling</td>
<td>Serum IgG &lt;135mg/dl</td>
<td>Histopathology: Not available or not diagnostic</td>
<td>No</td>
</tr>
</tbody>
</table>
HEREDITARY DISORDERS OF CONNECTIVE TISSUE DISEASES

• MARFAN’S SYNDROME

Blue sclera

• asymptomatic condition
• marked, generalised blue discolouration of sclera due to thinning.

▸ osteogenesis imperfecta.
▸ Marfan’s syndrome,
▸ Ehlers-Danlos syndrome,
▸ pseudoxanthoma elasticum,
▸ buphthalmos,
▸ High myopia and
▸ healed scleritis.
EMERGENCY EYE CONDITIONS IN RHEUMATIC DISEASES

ACUTE VISION LOSS
RED PAINFUL EYE
DIPLOPIA
WHEN TO SUSPECT A RHEUMATIC DISEASE......

- SUGGESTIVE HISTORY (INCL. FAMILY HISTORY)
- MANY / SYSTEMIC SYMPTOMS (FEVER, FATIGUE, ARTHRALGIA)
- OBVIOUS SIGNS (SKIN, NAILS, HAIR LOSS, PULSES)

**VASCUITIS**

- Nervous system
  - stroke
- Heart
  - myocardial infarction
  - hypertension
- Digestive system
  - bloody stool
  - abdominal pain
- Joints
  - pain
  - arthritis
- Skin
  - palpable purpura
  - livedo reticularis

- Eye
  - reduced visual acuity
- Nose
  - bleeds
- Lungs
  - bloody cough
  - lung infiltrates
- Kidneys
  - glomerular nephritis
- Muscle
  - pain

**Body Parts That Can Be Affected by Autoimmune Diseases**

- Brain
- Eyes
- Mouth
- Nerves
- Spinal Cord
- Thyroid
- Lung
- Stomach
- Joints
- Pancreas
- Large Intestine
- Small Intestine
- Bladder
- Vagina
DIAGNOSTIC WORK-UP

• FBC, ESR, CRP, RF, a-CCP, MSU
• ANA, a-dsDNA, ENA, ACL, LA1
• SACE
• C-ANCA/P-ANCA
• HLA B27, B51

• CHEST X-RAY
• CT
• MRI
• BIOPSY
TREATMENT OPTIONS

- TOPICAL
- NSAIDS
- STEROIDS
TREATMENT

- **TNF-α blockers**
  - Infliximab (*Remicade*)
  - Etanercept (*Enbrel*)
  - Adalimumab (*Humira*)
  - Certolizumab pegol (*Cimzia*)
  - Golimumab (*Simponi*)

- **Lymphocyte inhibitors**
  - Rituximab (*MABTHERA*)

- **Anti-interleukin antibodies**
  - Daclizumab (*Zenapax*)
  - Tocilizumab (*RO ACTEMRA*)

- **Anti-VEGF-A antibodies**
  - Ranibizumab (*LUCENTIS*)
  - Bevacizumab (*Avastin*)
DRUG TOXICITY

• Toxic Retinopathy
  • Chloroquine
  • Hydroxychloroquine

• Toxic Optic Neuropathy
  • Ethambutol
  • Isoniazid

• Papillitis
  • Cyclosporine

• Glaukoma
  • Steroids
SUMMARY